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Regions with Altered Degree Centrality and Their Functional Connectivity in First-Episode Drug-Naïve Major Depressive Disorder: A Resting-State Functional Magnetic Resonance Imaging Study

ABSTRACT

Objective: The aim of this study was to identify regions with altered degrees of centrality (DC) and changes in their functional connectivity (FC) in first-episode drug-naïve major depressive disorder (FEDN-MDD) patients using resting-state functional magnetic resonance imaging (fMRI).

Methods: The study included 74 FEDN-MDD patients who met the study criteria and 41 healthy controls (HCs). All had undergone fMRI scanning in the resting condition. To evaluate differences between FEDN-MDD patients and HCs, we first compared the DC between the 2 groups. The DC regions with the most significant differences were then taken as seeds, and their FC was calculated.

Results: Right posterior cingulum cortex (PCC.R), right precuneus (PCUN.R), and right putamen (PUT.R) all showed significantly different DC values ($P < .001$) between FEDN-MDD patients and HC groups, which helped in distinguishing these groups. The PUT.R in FEDN-MDD patients showed increased FC ($P < .001$) with the right inferior temporal gyrus and right inferior occipital gyrus compared to HC. Moreover, the PCUN.R in FEDN-MDD patients showed decreased FC ($P < .001$) with bilateral cerebellum crus I, left cerebellum crus II, bilateral orbital medial frontal gyrus, right superior medial frontal gyrus, left precuneus, left posterior cingulum cortex, right superior frontal gyrus, and PCC.R compared with the HC group. The *P*-values for cluster testing were .050, while for voxel testing they were .001.

Conclusion: These findings imply that PUT.R, PCUN.R, and PCC.R serve as the core brain net hub in FEDN-MDD patients, and their FC displays aberrant function. This may involve a specific psychiatric neuropathology associated with FEDN-MDD.

Keywords: Brain network, degree centrality, functional connectivity, major depressive disorder, resting-state fMRI

Introduction

Major depressive disorder (MDD) is characterized by severe, persistent, and unrelieved depression, anhedonia, helplessness, and guilt as the main symptoms. It is also accompanied by a range of other symptoms that affect the patient's social functioning, such as sleep disorders, suicidal ideation, and loss of appetite.[1-2] The incidence of MDD varies between countries with different cultures and religions, but MDD remains one of the most prevalent mental diseases worldwide. Major depressive disorder is the most common mood disorder in China, with a lifetime prevalence of 3.4% and a 12-month prevalence of about 2.1%.[3] A world burden study has estimated that MDD affects about 300 million people each year.[4] Major depressive disorder is often accompanied by self-injury and suicidal behavior and causes about 34.1 million years lived with disability (YLD). It is the fifth leading cause of YLD worldwide and

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seriously affects the patient's quality of life. However, the psychopathological changes in MDD are still not well known, especially with regard to brain network analysis.

Human brain functions are performed by the simultaneous activity of different intrinsic brain regions,[5] which may be the foundation for brain networks. Functional magnetic resonance imaging (fMRI) is one of the most widely used research methods to study human brain function. It is noninvasive, involves no radiation, and is amenable to repeat examination. The oxygen consumption by local brain regions is detected through changes in hemoglobin paramagnetism, thereby reflecting the activity of the corresponding brain region. Functional connectivity (FC) is often used to analyze the synchronous activity of a brain region network in the resting state.[6] Functional connectivity is based on the Pearson correlation, which correlates time-series signals from different brain regions to determine their working state simultaneously and while in the same state. time series is therefore a practical method for brain network analysis.

Graph theory is vital in the analysis of brain function as it allows quantitative examination of the connections between brain regions and the identification of key hubs, thus providing insights into how the brain processes information.[7] It also helps to understand abnormalities in brain connectivity that are associated with neurological and psychiatric disorders, thereby helping with diagnosis and treatment development. Zuo et al[8] proposed the following method for graph-based network analysis. Degree centrality (DC) evaluates the number of functional connections between voxels at the whole brain level using resting-state (RS) fMRI data, thereby evaluating the network centrality of the entire brain voxels. This provides the opportunity to conduct an unbiased general search without a prior hypothesis.[9] Furthermore, it is the most direct way to analyze central brain net nodes in the network and is considered a powerful method to detect the core brain net hub. Degree centrality calculates the relationship between specific voxels and functional connectomes of whole brain regions. In this way, deviations between seed point selection of the subjective region of interest and the actual data can be avoided, allowing more accurate results and reproducibility. The higher the DC value of a certain brain region, the more critical the role of that region as a node of the brain network hub. Researchers have used DC to probe the underlying psychopathology of mental illnesses. This revealed aberrant DC values in the left insula and bilateral hippocampus in patients with mild-to-moderate depression.[10] Adolescent MDD patients[11] also showed altered DC values in the bilateral fusiform gyrus, cingulate cortex, and superior parietal gyrus during first-episode schizophrenia.[12] Higher DC was reported in the somatosensory cortex of recovered anorexia patients,[13] while decreased DC in sensorimotor and auditory networks was found in patients with obsessive-compulsive disorder.[14] The combination of DC and FC allows the entire brain net composed of nodes and edges to be revealed in psychiatry studies, as well as providing an effective method for the study of brain function.

Therefore, the primary aim of this study was to identify altered core brain net hubs and their connected regions in the brain of first-episode drug-naïve (FEDN)-MDD patients. Our hypothesis is that by combining DC and FC, we can detect differences in instinct between brain networks in FEDN-MDD disease patients.

MAIN POINTS

- *Right putamen (PUT.R), right precuneus (PCUN.R), and right posterior cingulum cortex are the altered core hub of the brain network in first-episode drug-naïve major depressive disorder (FEDN-MDD) patients compared with healthy controls (HCs).*
- *Although these 3 regions did not show significant correlations with depressive symptom scores, they could distinguish FEDN-MDD patients from HCs.*
- *In FEDN-MDD patients, PUT.R showed increased functional connectivity (FC) with right inferior occipital gyrus and right inferior temporal gyrus, while PCUN.R showed decreased FC with bilateral cerebellum crus I, left cerebellum crus II, bilateral medial orbital frontal gyrus, right superior frontal gyrus, right medial middle frontal gyrus, left precuneus, left posterior cigulum cortex, and left superior frontal gyrus. Right posterior cingulum cortex showed significantly lower FC with PCUN.R compared to HCs. These results may identify the altered brain net in FEDN-MDD patients.*

Material and Methods

Participants

This study was approved by the Medical Research Ethics Committee of the Seventh People's Hospital of Hangzhou (No: 201509-1808). Written informed consent was obtained from all subjects before participation. First-episode drug-naïve major depressive disorder patients admitted to the Seventh People's Hospital of Hangzhou from January 2016 to June 2020 were eligible. All participants underwent diagnosis by a minimum of two experienced psychiatrists, with the inclusion criteria being: (1) first episode and received no prior treatment (including antidepressants, transcranial magnetic stimulation (TMS), and electroconvulsive therapy); (2) met the criteria for MDD from the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; (3) aged 18-60 years and right-handed; (4) fully understood the principle of the study and participated voluntarily. The exclusion criteria were as follows: (1) diagnosis of other mental illness, such as schizophrenia and bipolar disorder; (2) the presence of physical disease that may cause depression, such as brain tumor or neurodegenerative disease; (3) a history of substance dependence; (4) abnormal brain development; (5) patients who received antidepressant treatment, such as antidepressant drugs, modified ECT, and TMS; (6) patients in which members of their immediate family had other mental diseases; (7) patients who were unable to complete the fMRI scan, such as claustrophobic patients; (8) patients with completed fMRI scan, but the acquired data could not be used for analysis, due for example to head rotation >2° or lateral displacement >2 mm. The healthy control (HC) group was obtained after being accessed by at least 2 experienced psychiatrists and collection of their family history and past medical history. The same exclusion criteria as for the MDD group were applied. All subjects were tested with Hamilton Depression Rating Scale 24 items (HAMD-24) and RS-fMRI examination. The total HAMD-24 score in FEDN-MDD patients was >24 points, while the total score in HC participants was <7 points.

After applying the above criteria, a total of 115 subjects met the inclusion criteria, comprising 41 HC and 74 FEDN-MDD cases.

Acquisition of Magnetic Resonance Images

All subjects were scanned with the MRI scanner GE SIGNA™ HDXT1.5T MRI (General Electric, Milwaukee, Wisconsin, USA) instrument using a 8-channel head coil. Soundproof sponges and earplugs were used to reduce noise during equipment inspection and the subject's head movement. During examination, subjects were told to close their eyes, stay awake and relaxed, and try their best not to think about anything. Scanning parameters for the T1MPRAGE were as follows: TE 12 ms, TR 9.2 ms, FA15°, FOV 256 mm × 256 mm, slice thickness 1 mm, 256 slices, and total scanning time 5 minutes 28 seconds. The RS blood oxygen level dependent (BOLD) scanning sequence was as follows: TR 2000 ms, TE 40 ms, FA85°, FOV 240 mm × 240 mm, matrix 64 × 64, scanning layer thickness 4 mm without interval, number of layers 28, total scanning time 6 minutes. A total of 180 volumes of data were collected.

Resting-State Functional Magnetic Resonance Imaging Data Preprocessing

DPABI version 6.1 software,[15] based on the METLAB2018b platform was used for RS-fMRI data preprocessing and statistical analysis of fMRI data. Digital Imaging and Communications in Medicine (DICOM) data were first converted into Neuroimaging Informatics Technology Initiative (NIFTI) format. The first 10-time-series data were removed in order to prevent errors caused by gradient magnetic field instability. New Segment + Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) were used for image segmentation. Affine normalization of data was performed according to European templates in the software. Noise covariates, including white matter and cerebrospinal fluid, were removed, and the filtering range was set from 0.01 to 0.1 Hz. DARTEL was used for standardization. The DC was calculated, with the threshold set at 0.25. The results were smoothed with the smoothing parameter (full width at half maxima) established to 6 × 6 × 6 mm^3. The formula used for the calculation of DC[16] was:

$$R_{ij} = \frac{\sum\left[\left(\chi[t]_i - \bar{x}_i\right)\left(\chi[t]_j - \bar{x}_j\right)\right]}{\sqrt{\sum\left[\left(\chi[t]_i - \bar{x}_i\right)^2\left(\chi[t]_j - \bar{x}_j\right)^2\right]}}$$

$$t = 0\ldots T, \mathrm{i} = 1\ldots N, \mathrm{j} = 1\ldots N,$$

Statistical Analysis

We first extracted the signal values for specific brain regions that showed significant differences according to the Montreal neurology institute (MNI) coordinates. Summary statistics were computed for all relevant variables, using mean (SD) to indicate the distribution characteristics of numerical variables and using percentages to represent categorical variables. Statistical Package for the Social Sciences Statistics version 20.0 software (IBM SPSS Corp.; Armonk, NY, USA) was used to perform Kolmogorov–Smirnov analysis for all numerical variables in this experiment. All the numerical variables data from this study conformed to the characteristics of a normal distribution. The *t*-test was used to compare groups, Pearson correlation coefficient analysis was used to evaluate the correlation between 2 variables, and the χ^2 test was used for the categorical variables. Receiver operator characteristic (ROC) curve was used to determine the discriminatory capacity of DC for distinguishing FEDN-MDD patients from HC. The GraphPad prism software version 9.5, was used for generating statistical graphs.

The preprocessed fMRI data was subjected to a *t*-test for group comparison, and the results were corrected for multiple comparisons using Gaussian random field (GRF) correction. The voxel *P*-value of .001 and the cluster *P*-value of .050 were employed. A significance level of $P < .050$ was considered to indicate a significant difference. The brain regions showing significant DC differences between the 2 groups, based on the anatomical automatic labeling template, were extracted using MNI space coordinates. These coordinates were utilized as seeds to compute the FC of the brain regions. Differences in FC between the 2 groups were analyzed using a *t*-test, and multiple comparison correction was applied using GRF.

BrainNet Viewer software (https://www.nitrc.org/projects/bnv/)[17] was used to set the MNI coordinates of DC and FC differential brain regions as the node coordinates. The voxel numbers of DC and FC differential brain regions were designated as the node's size, and the FC value between seed points and FC differential brain regions was set as the edge value.

Results

There were no significant differences observed between the FEDN-MDD and HC groups in terms of age ($P = .355$), gender ($P = .774$), and education level ($P = .573$), with HAMD-24 scores being the exception ($P < .001$) (Table 1).

Differential Degree Centrality Brain Regions

First-episode drug-naïve major depressive disorder patients showed significantly increased DC values for right putamen (PUT.R) ($P < .001$) compared to HC, whereas the DC values for right precuneus (PCUN.R) ($P < .001$), and right posterior cingulum cortex (PCC.R) ($P < .001$) were significantly decreased. The positions of these differential brain regions are shown in Table 2 and Figure 1.

Table 1. Demography and Mental State Assessment of Participants

	FEDN-MDD	HC	*P*
Age (years)	27.689 (SD = 9.237)	29.317 (SD = 8.551)	.355
Gender (male/female)	24.3%/75.7%	22.0%/78.0%	.774
Education (years)	13.324 (SD = 2.221)	13.585 (SD = 2.617)	.573
HAMD-24 score	26.052 (SD = 3.387)	2.226 (SD = 1.343)	<.001

FEDN-MDD, first-episode drug-naïve major depressive disorder; HAMD-24, Hamilton Depression Rating Scale (24 items); HC, healthy control.

Table 2. Degree Centrality Differential Brain Regions and Their Montreal Neurological Institute Coordinates

	Peak MNI Coordinates				
Brain Region (AAL)	*X*	*Y*	*Z*	Voxel	*P* (GRF)
PUT.R	33	−12	3	30	Cluster < .050, voxel < .001
PCUN.R	9	−48	18	28	Cluster < .050, voxel < .001
PCC.R	6	−43	28	20	Cluster < .050, voxel < .001

AAL, anatomical automatic labeling; GRF, Gaussian random field correction; MNI, Montreal Neurological Institute; PCC.R, right posterior cingulum cortex; PCUN.R, right precuneus; PUT.R, right putamen.

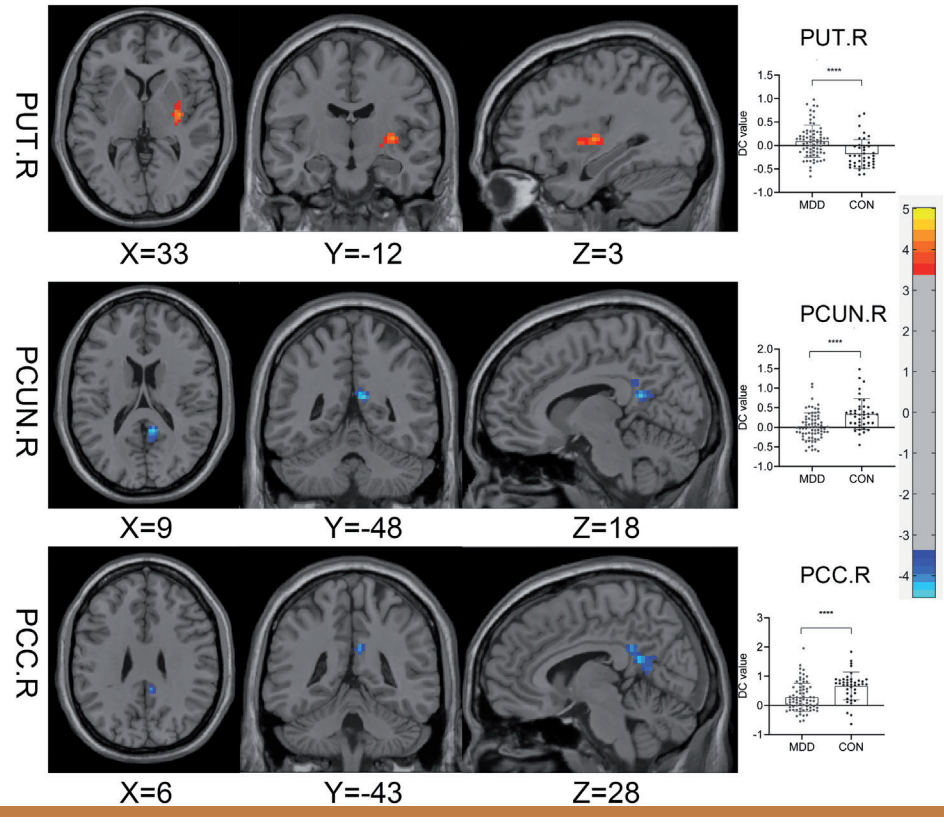

Figure 1. Differential DC brain regions between FEDN-MDD and HC groups. First-episode drug-naïve major depressive disorder patients showed altered DC regions in the PUT.R, PCUN.R, and PCC.R compared to the HC group. Their peak MNI coordinates in the *X*, *Y*, and *Z* coordinates in the MNI space are labeled separately below. The right-hand side shows a point diagram of the mean values for the differential regions between the 2 groups. ** indicates significance at the .001 level. The color bar shows only the values with significant differences. DC, degree centrality; HC, healthy controls; FEDN-MDD, first-episode drug-naïve major depressive disorder; MNI, Montreal Neurological Institute; PCC.R, right posterior cingulum cortex; PCUN.R, right precuneus; PUT.R, right putamen.**

Correlation of Degree Centrality Values and Depression Symptoms

Pearson correlation analysis was used to determine the correlation between HAMD-24 scores and DC values in the differential brain regions described above. No significant correlations were found between HAMD-24 with PUT.R, PCUN.R, and PCC.R ($P = .403$, $P = .332$ and $P = .455$, respectively) (Table 3).

Ability of Degree Centrality to Distinguish First-Episode Drug-Naïve Major Depressive Disorder Patients from Healthy Controls

The ROC of DC values for PUT.R, PCUN.R, and PCC.R and for all 3 regions combined were 0.744, 0.739, 0.736, and 0.777, respectively. The sensitivities were 78.38%, 63.15%, 81.08%, and 75.68, respectively. The specificities were 65.85%, 78.05%, 65.85%, and 73.17%, respectively. Finally, Youden's *J* indexes were 44.23, 41.56, 46.93, and 48.85, respectively (Table 4 and Figure 2).

Table 3. Pearson Correlation Between Hamilton Depression Rating Scale (24 items) Scores and Differential Brain Region Degree Centrality Values

HAMD-24	Pearson Correlation Coefficient	*P*
PUT.R	0.075	.403
PCUN.R	0.087	.332
PCC.R	0.067	.455

HAMD-24, Hamilton depression rating scale (24 items); PCC.R, right posterior cingulum cortex; PCUN.R, right precuneus; PUT.R, right putamen.

Different Functional Connectivity with the Degree Centrality Regions As Seed Points

The differential brain regions of DC shown in Table 2 were used as seed points to compare FC differences between the FEDN-MDD and HC groups. The FC between PUT.R and the right inferior occipital gyrus (IOG.R) and between PUT.R and the right inferior temporal gyrus (ITG.R) were both increased in FEDN-MDD cases compared to HC. However, the FC between PCUN.R and the bilateral cerebellum crus I, left cerebellum crus II, bilateral medial orbital frontal gyrus (medOFG.L/R), right medial superior frontal gyrus, left precuneus (PCUN.L), left posterior cingulum cortex, and right superior frontal gyrus (SFG.R) was all lower in FEDN-MDD patients compared to HC (Table 5 and Figure 3).

Discussion

The graph-based DC and the FC methods were integrated in this study and used to compare the connective patterns of brain regions between FEDN-MDD and HC subjects. We first computed brain network hub abnormalities in FEDN-MDD patients by DC at the voxel level. Patients with FEDN-MDD showed significant alterations in DC values for PUT.R, PCUN.R, and PCC.R compared to HC. We then

Table 4. Discrimination Ability of the Degree Centrality

Brain Region	AUC	*P*	SEM-AUC	95% CI	Sensitivity (%)	Specificity (%)	Youden's *J* Index
PUT.R	0.744	<.001	0.050	0.647-0.842	78.38	65.85	44.23
PCUN.R	0.739	<.001	0.047	0.647-0.831	63.15	78.05	41.56
PCC.R	0.736	<.001	0.050	0.639-0.834	81.08	65.85	46.93
Combined	0.777	<.001	0.045	0.689-0.865	75.68	73.17	48.85

AUC, area under the curve; PCC.R, right posterior cingulum cortex; PCUN.R, right precuneus; PUT.R, right putamen; SEM-AUC, standard error of mean of AUC.

used these differential brain regions as seed points for FC analysis. Our results showed the FC between PUT.R and IOG.R, and between PUT.R and ITG.R, was significantly greater in FEDN-MDD patients than in HC. In contrast, the FC between PCUN.R and the bilateral cerebellum crus I, left cerebellum crus II, bilateral medOFG.L/R, SFG.R, right medial middle frontal gyrus, PCUN.L, PCG.L, left superior frontal gyrus (SFG.L), and PCG.R was significantly lower in FEDN-MDD patients than in HC.

The Altered Core Brain Net Hub in First-Episode Drug-Naïve Major Depressive Disorder Patients

Putamen forms part of the lentiform nucleus and together with the caudate nucleus constitutes the striatum. Neuroanatomical studies have shown that PUT is involved in many important brain activities, including reward, cognitive function, addiction, and language function.[18] Putamen function is abnormal in many disease states such as Parkinson's disease,[19] Alzheimer's disease,[20] depression,[21] obsessive-compulsive disorder,[22] and chronic pain.[23] It is also an essential structure in the brain's reward circuit in MDD.[24] Specifically, fMRI studies have found that PUT is significantly activated when the reward is expected.[25] This function may be related to anhedonia (loss of pleasure and reward-seeking behavior)[26] and to developmental periods in MDD.[27] However, another fMRI study found that spontaneous neuron activity in the right putamen was higher during the initial and remission periods in MDD patients than in HC.[28] This appears to be a characteristic of depression that is different from other emotional disorders. A dynamic analysis of MDD brain activity found that MDD patients had a significantly higher dynamic amplitude of low-frequency upgrade in PUT than HC.[29] This is a characteristic change in MDD.

In addition to being anatomically part of the parietal lobule, PCUN is a crucial component of the human default network[30] and can be significantly activated during memory retrieval,[31] reward monitoring,[29] and emotion processing.[32] Rosa et al[33 found] that PCUN was important in both resting and task states.[34] The spontaneous activity of both PCUN.R and SFG.L is abnormal in MDD.[35] The combination of PCUN and OFG is a vital brain region for emotion processing in primates, including humans.[36] This brain region is involved in the evaluation of anticipated rewards and is closely associated with both emotion and executive function.[37]

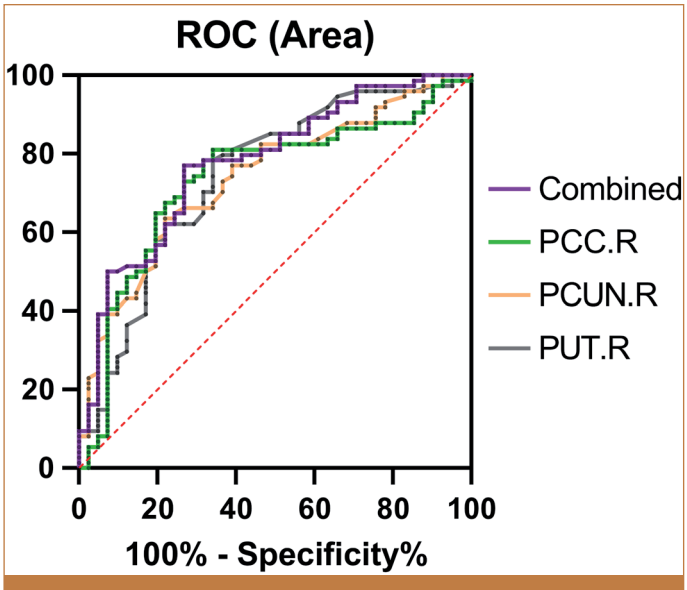

Figure 2. ROC analysis of the DC values. DC, degree centrality; PCC.R, right posterior cingulum cortex; PCUN.R, right precuneus; PUT.R, right putamen; ROC, receiver operating curve.

Table 5. Differences in Functional Connectivity Connections with Seed Points

	Peak MNI Coordinates				
Brain Region (AAL)	*X*	*Y*	*Z*	Voxel	*P* (GRF)
PUT.R (seed 1)	33	−12	3	30	
IOG.R	24	−87	−3	21	Cluster < .050, voxel < .001
ITG.R	45	−57	−6	31	Cluster < .050, voxel < .001
PCUN.R (seed 2)	9	−48	18	28	
Cerebelum Crus 1.L	−21	−87	−24	39	Cluster < .050, voxel < .001
Cerebelum Crus 1.R	27	−84	−24	53	Cluster < .050, voxel < .001
Cerebelum Crus 2.L	−17	−90	−27	28	Cluster < .050, voxel < .001
medMFG.L	−5	70	−3	17	Cluster < .050, voxel < .001
medMFG.R	3	63	−9	32	Cluster < .050, voxel < .001
medOFG.R	3	61	4	21	Cluster < .050, voxel < .001
PCUN.L	−2	−56	31	62	Cluster < .050, voxel < .001
PCC.L	−6	−43	31	26	Cluster < .050, voxel < .001
SFG.R	15	33	51	49	Cluster < .050, voxel < .001
PCC.R (seed 3)	6	−43	28	20	
PCUN.R	9	−57	33	94	Cluster < .050, voxel < .001

AAL, anatomical automatic labeling; GRF, Gaussian random field correction; IOG.R, right inferior occipital gyrus; ITG.R, right inferior temporal gyrus; L, left side; medMFG, medial middle frontal gyrus; MNI, Montreal Neurological Institute; medOFG, medial orbital frontal gyrus; PCC.L, left posterior cingulum cortex; PCC.R, right posterior cingulum cortex; PCUN.L, left precuneus; PCUN.R, right precuneus; PUT.R, right putamen; R, right side; SFG.R, right superior frontal gyrus.

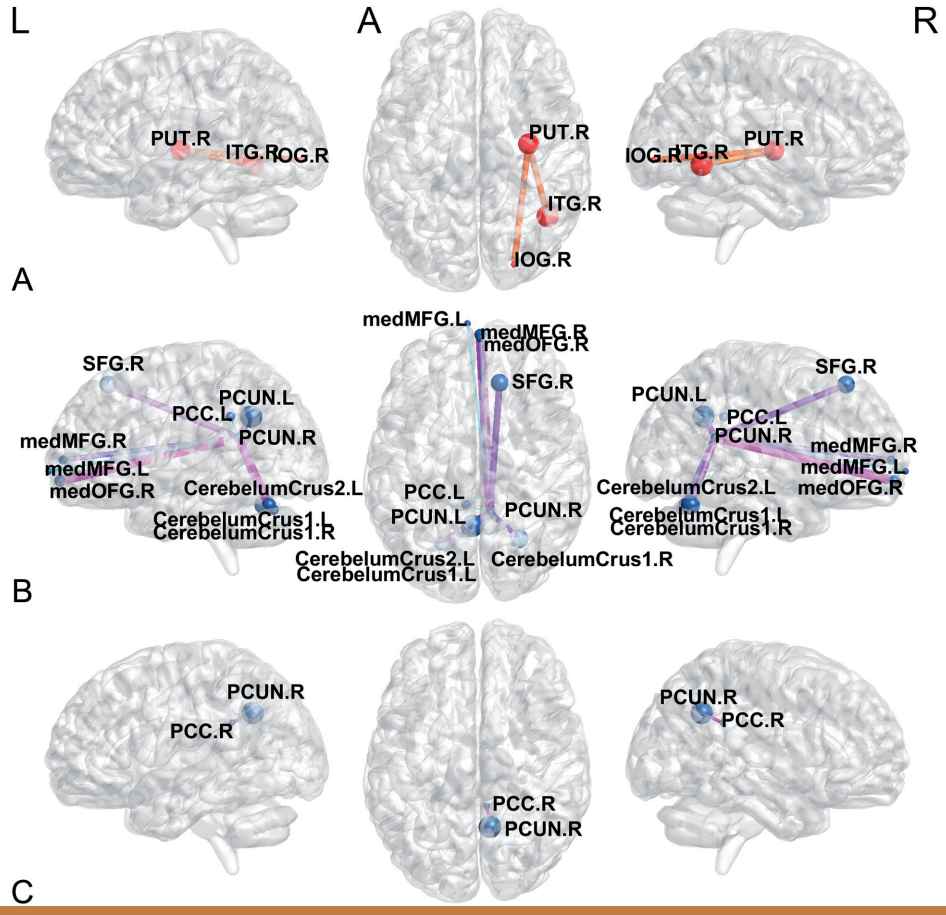

Figure 3. FC differential brain regions of each seed point and FC differential regions between seed regions (A: anterior, L: left side, R: right side). Panel A shows the result with PUT.R as seed. Panel B shows the results with PCUN.R as seed. Panel C shows the results with PCC.R as seed. The node's size was set according to the absolute value of the voxel number of the region, while the edge's size was set according to the absolute value of the FC between the 2 regions. FC, functional connectivity; IOG.R, right inferior occipital gyrus; ITG.R, right inferior temporal gyrus; L, left side; medMFG, medial middle frontal gyrus; medOFG, medial orbital frontal gyrus; PCC.L, left posterior cingulum cortex; PCC.R, right posterior cingulum cortex; PCUN.L, left precuneus; PCUN.R, right precuneus; PUT.R, right putamen; R, right side; SFG.R, right superior frontal gyrus.

The PCC.R core brain net region showed significantly lower DC in the current study of FEDN-MDD. The PCC participates in critical neural networks related to human consciousness and is an essential structure for maintaining consciousness and for information processing.[38] The PCC and PCUN jointly perform the critical function of self-reflection of consciousness, which needs to pause in order to engage in complex cognitive and sensory information processing. The PCC is also the structure with the highest metabolism in the brain,[39] and PCC dysfunction leads to abnormal learning and memory function in humans, especially in MDD.

Altered Functional Connectivity with the Core Brain Net Hub in First-Episode Drug-Naïve Major Depressive Disorder Patients

The IOG.R and ITG.R were found to have more robust connectivity with PUT.R in this study of FEDN-MDD. The IOG is part of the occipital lobe and is related to the human vision process,[40] such as face recognition[41] and facial feature cognition[42] in social activities. Neuroanatomy investigations have found that IOG can directly receive signal projection from the center of the retina[43] and jointly perform the face recognition function by cooperating with other facial recognition areas, such as the fusiform face area.[44] However, the recognition function of facial expressions is impaired in MDD patients.[45] Other than accurate recognition of happy faces, MDD patients cannot easily recognize fear, sadness, anger, surprise, or disgust, meaning that cognitive function of negative emotions can be easily confused with one of the other emotions. The ITG is part of the temporal lobe and is involved in visual processing,[46] early visual arousal,[47] and optical object recognition.[48] The ITG is also related to emotional processing by connecting with the limbic system through the superior longitudinal tract, thereby playing an essential role in emotional processing.[49] A voxel-based study in MDD patients found that asymmetry in bilateral ITG gray matter was associated with depressive symptoms[50] and that gray matter volume in ITG.R was reduced compared with contralateral ITG. Inferior temporal gyrus also plays a role in other psychotic conditions. In patients with somatization disorders, increased FC in the right ITG correlated positively with the severity of anxiety symptoms.[51] Moreover, ITG.R activity in high-alexithymia patients increased dramatically when exposed to crisp emotional stimuli,[52] indicating its involvement in emotional expression and emotion processing. The increased FC between PUT.R and IOG.R and between

PUT.R and ITG.R may indicate an inner desire of FEDN-MDD patients to seek a specific person or emotional stimuli to obtain pleasure and rewards and to reduce self-denial and negative emotions.

With regard to PCUN.R connections, weaker FC was found in the frontal lobe, cerebellum, PCC, and contralateral PCUN. The frontal lobe has been widely studied in mental illness and especially in MDD. It participates in cognitive function and emotional processes, and different subregions may have different roles. The OFG participates in the reward–punishment network through the habenula nucleus,[53] and influences the activity of serotonin-containing neurons, which are the target of antidepressants. The habenula nucleus also projects dopamine-containing neurons through the rostral-medial tegmental nucleus, thus regulating the reward–punishment network. The medOFG maintains the non-reward attraction state of MDD, thereby generating related memories via its error neurons.[54] The MFG.R monitors other frontal lobe settings and the brain's executive function.[55] The MFG volume decreases in MDD patients and is related to the course of the disease.[56] Chronic stress during the occurrence and development of MDD is also associated with abnormal MFG function, consistent with the predictions of the pressure-sensitive model for MDD. The SFG region is involved in multiple brain activities, including motor control, working memory, resting state, and cognitive control. Autopsy studies have shown that SFG interacts with the inferior frontal gyrus, cuneus, lingual gyrus, parietal lobule, precuneus, and contralateral SFG through white matter fiber bundles.[57] A voxel-based meta-analysis showed that SFG function was abnormal in MDD patients, which could therefore be a pathophysiological change in emotional disorders.[58] It should also be noted that PCUN.R shows decreased FC in some cerebellar brain regions involved in motor regulation, posture maintenance, and emotional and cognitive processing in humans.[59] The RS FC of the cerebellum and brain is lower in MDD.[60] Specifically, crus I and II showed reduced FC of the executive function network, default network (DMN), and limbic system network related to emotion. The PCC has been intensively studied in MDD in relation to human executive function[61] and attempted suicide.[62] Interestingly, the PCC serves as a central hub in the brain's network and connects with other regions, thus forming a neural network. To summarize these findings, the PCUN.R and PCC.R comprise a complex network that may influence the human emotional process and related behavior such as anhedonia, reduced movement, and attempted suicide.

The present study found decreased FC between bilateral PCUN and PCC and multiple brain regions in the prefrontal lobe, constituting the DMN. Default network activity tends to decrease during attentional brain tasks and increase during tasks such as memory or abstract thinking.[63] A meta-analysis found that FC among subsystems of DMN was decreased during MDD, but this reduction did not correlate significantly with the course of MDD or treatment, clinical symptoms, and trait rumination.[64] Another meta-analysis also concluded the FC between rumination and the DMN subsystem was not significantly correlated.[65] Voxel-mirrored homotopic connectivity analysis of MDD patients found that FC was reduced between the anterior subnetwork of DMN and the posterior cerebellar lobe.[66] Different regions in the human brain interact with each other to perform specific functions in the form of neural circuits. These circuits are abnormal in neuropsychiatric disorders. For example, the limbi c-cortico-striatal-thalamic-cortical (LCSTC) loop shows abnormal function in affective disorders[67] and is associated with depression. Brain regions with abnormal FC, such as PUT, PCUN, and PCC, and prefrontal brain regions were found to be involved in LCSTC. This is consistent with some of the results from the present study.

No significant correlations were found here between the DC values of PUT-R, PCUN.R, and PCC.R and the HAMD-24 scores in FEDN-MDD patients. This could be because the DC values focus on the role of these regions as net hub nodes in the brain network.[68] However, the abnormalities of critical nodes in the FEDN-MDD brain network and FC found in this study may still represent a specific neuropsychiatric change in these patients.

Some studies on DC have reported results that are inconsistent with our findings. Chen et al[10] found that intrinsic abnormality of the brain in patients with mild-to-moderate depression was mainly located in the PCUN and insular. Guo et al[69] found increased DC in the bilateral insula and left lingual area of MDD patients, together with reduced DC in the right cerebellum and bilateral superior parietal lobe.[69] Moreover, the DC values were not significantly correlated with disease severity or duration. These discrepancies may be due to differences in the age and degree of depressive severity between study cohorts as well as due to differences in the RS-fMRI scanning protocol and multicorrection methods.

Limitations

This study has several limitations. First, the sample size was relatively small and derived from a single hospital. Therefore, the conclusions are somewhat limited and need further verification using larger, multicenter patient cohorts. In addition, fMRI data were obtained using the 1.5T MRI scanner, and hence the signal-to-noise ratio is relatively low. Nevertheless, the 1.5T MRI scanner is widely available and thus may benefit more people due to its lower price and greater accessibility.

Availability of Data and Materials: *The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.*

Ethics Committee Approval: *This study was approved by Ethics Committee of the Seventh People's Hospital of Hangzhou (Approval No: 201509-1808, Date: September 9, 2015).*

Informed Consent: *Written informed consent was obtained from the patients who agreed to take part in the study.*

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